

Factors Affecting Water Vapor Transmission through Free Polymer Films

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Abstract □ Water vapor permeation studies were carried out on cast and sprayed polymer films. The polymers used were cellulose acetate phthalate and *n*-butyl methacrylate. Significant differences in permeability behavior were observed with the cellulose acetate phthalate films, depending on whether moisture was present on one or both sides of the film during permeation. This effect did not occur with the *n*-butyl methacrylate films. These data, together with results on water uptake by cellulosic films, suggest that dehydration of the distal cellulose acetate phthalate film surface occurs when moisture is present only on the proximal surface. The effect has potential significance in the design of water vapor permeation tests on hydrophilic films. No differences were observed between the water permeation properties of sprayed and cast cellulose acetate phthalate films.

Keyphrases □ Polymer films, free—factors affecting water vapor transmission □ Water vapor transmission—free polymer films, factors involved □ Permeation, water vapor—cast and sprayed polymer films, factors involved

In the past 10–15 years, polymers have been used increasingly as coatings for solid pharmaceutical dosage forms to facilitate product differentiation and appeal, to envelop unpleasant odors and tastes, and to protect the active ingredient and the dosage form against adverse environmental conditions. One important property of the coating in the last regard is its ability to protect the dosage forms from attack by atmospheric moisture, thereby increasing the life of a pharmaceutical compound or formulation susceptible to hydrolytic decomposition. It is, therefore, of importance to know to what degree moisture uptake is retarded by the application of polymer film coats to solid dosage forms.

The usual method for determining the polymer of choice for film coating is through tests carried out on free (*i.e.*, nonapplied) polymer films. These tests, in which thickness, temperature, film formulation, *etc.*, are varied, are designed to assess the ability of the free film to retard moisture permeation.

Previous communications (1, 2) reported studies in which moisture permeation of polymer films was observed under conditions of a finite to zero vapor pressure gradient. It was shown that the permeability constant for lipophilic films is virtually independent of film thickness and, as expected, increases with temperature. Furthermore, sorption of water vapor by the films does not occur to any appreciable extent. In contrast, the permeability coefficient for hydrophilic films increases markedly with film thickness and, for a given film thickness and vapor pressure gradient, varies inversely with temperature. In further contrast, the affinity of the water molecules for the polymer matrix leads to significant water vapor sorption which, in turn, acts to plasticize the film.

It was suggested (2) that dehydration of the hydrophilic films may account for the decrease in permeation

at higher temperature. If this is the case, then differences should be seen when water vapor, under the same pressure gradient, is present on both sides of the film. No significance has apparently been attached to this possibility in the earlier film permeation studies reported in the literature.

An additional factor of interest, and possible concern, when making permeability comparisons between different film systems is the method of preparation of the film. Most commonly, free polymer films are prepared by either pouring (casting) or spraying a solution of the polymer in a volatile solvent onto a suitable surface. After the solvent evaporates, the residual films are removed and used for study. It is conceivable that the method of preparation might lead to differences in molecular orientation within the film which could, in turn, affect moisture permeability. This possibility, as well, has not apparently received attention in the literature.

Accordingly, this paper is concerned with: (a) the permeability characteristics of both hydrophilic and lipophilic polymer film systems, in which water vapor is present on one and on both sides of the film; and (b) the effect of the manner of film preparation on the permeability characteristics of hydrophilic films.

EXPERIMENTAL

Preparation of Cast Films—Various amounts of cellulose acetate phthalate¹ and *n*-butyl methacrylate² polymer solutions were poured onto glass plates on which were placed glass rings, of known diameter, to control the area of spreading. The compositions of the two polymer solutions were:

Hydrophilic Film	Amount
cellulose acetate phthalate	50 g.
diethyl phthalate ³	12.5 g.
acetone ³	400 ml.
methylene chloride ³ , <i>q.s.</i>	1000 ml.
Lipophilic Film	
<i>n</i> -butyl methacrylate	100.0 g.
diethyl phthalate	2.5 g.
acetone–methylene chloride (1:1), <i>q.s.</i>	1000 ml.

The solvents were allowed to evaporate overnight; the films were then removed and placed in a desiccator until required. Film thickness was at first measured by both density determinations and the use of calipers. However, since the thickness values obtained by the two methods were found to be within 3% of each other, all subsequent determinations were carried out with the calipers.

Preparation of Sprayed Films—A solution of cellulose acetate phthalate was sprayed onto vertical glass plates, using a spray gun

¹ Eastman Organic Chemicals.

² Dupont Elvacite 2044.

³ Reagent grade.

Table I—Permeability Properties of Sprayed and Cast Cellulose Acetate Phthalate Films

Film System	Temperature	$P^0 \times 10^{-7}$, g./hr./cm./mm. Hg
Cast film; moisture on one side of film	20°	1.34 ± 0.55 ^a
	30°	1.30 ± 0.21
	40°	1.06 ± 0.47
Cast film; moisture on both sides of film	20°	1.60 ± 0.89
	30°	2.37 ± 0.98
	40°	3.69 ± 0.89
Sprayed film; moisture on both sides of film	20°	1.90 ± 0.43
	30°	2.41 ± 0.71
	40°	3.53 ± 1.12

^a 95% confidence interval.

operating at a pressure of 2 p.s.i. The spray nozzle was adjusted so that a uniform coverage, 2.5 cm. in diameter, was produced at a distance of 15 cm. Between spray cycles, the glass plates were heated to offset the cooling effect created as the film dried. The composition of the film solution used was:

Hydrophilic Film	Amount
cellulose acetate phthalate	50 g.
acetone	675 ml.
ethanol ³	25 ml.
diethyl phthalate	12.5 g.
methylene chloride, <i>q.s.</i>	1000 ml.

The films were left overnight; they were then removed from the glass plates and stored in a desiccator until required.

Permeation Studies—The permeation cell was similar to that used by Patel *et al.* (3) and consisted of a 34-ml. vial with a 1.7-cm. hole in the center of the cap. The film, cut to the appropriate size, was placed between two rubber gaskets, 1.9-cm. i.d., which were fitted inside the cap. Following the addition of 10 ml. of an appropriate saturated salt solution, the cap containing the film and gasket was screwed onto the vial.

The transmission cells and a single-pan analytical balance were placed inside a temperature-controlled oven. The vapor pressure conditions on the proximal film surface within the cell (vp_{proximal}) were controlled by the use of saturated solutions of various inorganic salts (4). Water vapor conditions on the distal film surface outside the cell (vp_{distal}) ranged from zero upward. In this manner, studies were carried out in which water vapor was present on one and both sides of the polymer membrane. In the former case, sufficient desiccant was placed inside the oven so that vp_{distal} equaled zero. In the latter case, saturated salt solutions were used to control vp_{distal} to a known value. In all studies described, the vapor pressure gradient ($ep_{\text{proximal}} - vp_{\text{distal}}$) was held at 16.4 (±0.3 SE) mm. Hg.

The weight loss of the cell as a function of time was determined directly by means of the balance within the oven. The steady-state rate (dw/dt) was determined, where dw is the weight loss in grams with time in hours, dt . Under these conditions, the amount of water entering the proximal surface equals the amount evaporating from the distal surface. To ensure that all weight losses were due only to water vapor transmission through the polymer films under investigation, experiments were conducted using aluminum disks as

Table II—Permeability Properties of Cast *n*-Butyl Methacrylate Films

Film System	Temperature	P , g./hr./cm./mm. Hg
Moisture on one side of film; film thickness = 22.0×10^{-3} cm.	20°	1.92 ± 0.60 ^a
	25°	2.22 ± 0.12
	35°	3.16 ± 0.32
	40°	3.43 ± 1.30
Moisture on both sides of film; film thickness = 6.0×10^{-3} cm.	20°	2.04 ± 0.28
	30°	2.59 ± 0.22
	40°	3.46 ± 0.46

^a 95% confidence interval.**Table III**—Amount of Water in Cast Cellulose Acetate Phthalate Films as a Function of Temperature

Film System	Temperature	g. Water/100 g. Polymer
Moisture on one side of film	20°	4.06 ± 0.51 ^a
	30°	1.85 ± 0.10
	40°	0.58 ± 0.20
Moisture on both sides of film	20°	4.00 ± 0.30
	30°	3.02 ± 0.29
	40°	2.39 ± 0.15

^a 95% confidence interval.

“blanks” in place of the film. No weight loss was observed under these conditions.

The permeability constant, P , was calculated from the following equation, as developed by Meares (5) from a consideration of Fick's first law of diffusion and Henry's law:

$$P = [dw/dt \times l] / [(vp_{\text{proximal}} - vp_{\text{distal}}) \times A] \quad (\text{Eq. 1})$$

where l is the film thickness in cm., and A is the exposed film area in cm.². P has the units g. hr.⁻¹ cm.⁻¹ mm. Hg.⁻¹. Because P varies with l in the case of hydrophilic films, such as cellulose acetate phthalate, the permeability constants were determined at several thicknesses and the data were then represented by the following equation:

$$P = (dP/dl) + P^0 \quad (\text{Eq. 2})$$

where P^0 corresponds to a theoretical thickness-independent permeation process such as is found with lipophilic film systems. Thus, with *n*-butyl methacrylate systems, $dP/dl = 0$ and, hence, $P = P^0$.

The amount of water in cellulose acetate phthalate films at different temperatures was obtained by weighing the films prior to a run, when they were completely dried, and immediately after a run, when equilibrium moisture content conditions were in effect.

RESULTS AND DISCUSSION

The permeation data for cellulose acetate phthalate films are presented in Table I; those for *n*-butyl methacrylate are listed in Table II. Examination of Table I shows that there is a significant difference in the permeability behavior of cast cellulose acetate phthalate films, depending on whether water vapor is present on one or both sides of the film during the study. With moisture present on both sides, P^0 increases with temperature. When water vapor at the distal film surface is held at zero (*i.e.*, moisture is present on only one side), P^0 shows an apparent decrease with increasing temperature, an effect observed previously (2). These data must be compared with those for *n*-butyl methacrylate films where, as seen in Table II, under similar vapor pressure gradients to those employed with the cellulose acetate phthalate films, P increases with temperature, irrespective of whether or not water vapor is present on one or both sides of the film.

The behavior described may be rationalized on the basis of differing degrees of hydration of cellulose acetate phthalate films, brought about by the conditions used to generate a certain vapor pressure gradient. Little or no sorption occurs when water vapor permeates *n*-butyl methacrylate films; therefore, no dehydration can occur as the temperature is raised. Consequently, it is to be expected that the permeability characteristics of such films are independent of the absence or presence of moisture at the distal film surface. Moisture uptake does, however, occur with cellulose acetate phthalate films when water is the permeant. When water vapor is present on both sides of the film, dehydration does not occur as the temperature is raised, and the relative changes in P^0 with temperature closely resemble the temperature-produced changes in P that are found with *n*-butyl methacrylate films. Only when vp_{distal} is maintained at zero does dehydration become a factor in moisture permeation through cellulose acetate phthalate films and lead to a reduction in P^0 with increasing temperature (2). Presumably, under such conditions, the distal film surface is dehydrated to a degree depending on the temperature. Increasing dehydration (or desorption) in a hydrophilic polymer is equivalent to deplasticization, and the result is an apparent reduction in the permeation process.

This discussion is supported by determinations of the amount of water in cellulose acetate phthalate films having moisture on one or both sides of the film (Table III). It is apparent that when $v_{p_{\text{distal}}}$ is held at zero, the amount of water in the cellulose acetate phthalate film decreases at a faster rate with increasing temperature than when $v_{p_{\text{distal}}}$ has a finite value and moisture is present on both sides of the film.

The question as to whether cast films differ from sprayed films of the same polymer system in their water vapor transmission properties is resolved from a consideration of Table I. It is apparent that there is no significant difference between the values of P^0 for each system at the three temperatures studied.

SUMMARY AND CONCLUSIONS

This work demonstrated that significant permeation differences from expected behavior exist with hydrophilic cellulose acetate phthalate films when the atmosphere adjacent to the distal surface of the film is devoid of water vapor. No such effect is observed with lipophilic *n*-butyl methacrylate films. This anomalous effect, which increases with increasing temperature, is due to partial dehydration of the cellulose acetate phthalate film. This factor should be kept in mind when developing realistic testing conditions for evaluating the water vapor permeation properties of free hydrophilic films, especially if extrapolation to coated solid dosage forms is anticipated.

The results also show that the method of film preparation, be it casting or spraying, does not affect the permeation characteristics of cellulose acetate phthalate films.

REFERENCES

- (1) G. S. Banker, A. Y. Gore, and J. Swarbrick, *J. Pharm. Pharmacol.*, **18**, 457(1966).
- (2) J. Swarbrick and A. H. Amann, *ibid.*, **20**, 886(1968).
- (3) M. Patel, J. M. Patel, and A. P. Lemberger, *J. Pharm. Sci.*, **53**, 286(1964).
- (4) "International Critical Tables, III," McGraw-Hill, New York, N. Y., 1928, pp. 248-292.
- (5) P. Meares, "Polymer Structure and Bulk Properties," Van Nostrand, New York, N. Y., 1965, pp. 257-274.

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Colorimetric Estimation of Cephalexin, Cephaloglycin, and Related Compounds

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Abstract □ A specific color reaction is described for the colorimetric estimation of cephalosporin derivatives having the following intact side chain in the 7-position: $\text{RCH}(\text{NH}_2)\text{CO}-$, R being a heterocyclic or aromatic ring. The method is applicable for the detection of cephaloglycin (or desacetyl cephaloglycin) or cephalexin in urine. Penicillin analogs respond to the test, but the sensitivity is much less.

Keyphrases □ Cephalexin and related compounds—colorimetric estimation □ Cephaloglycin and related compounds—colorimetric estimation □ Colorimetry—estimation of cephalexin, cephaloglycin, and related compounds

A specific colorimetric test was developed for the determination of cephalosporin derivatives having the following intact side chain in the 7-position: $\text{RCH}(\text{NH}_2)\text{CO}-$, R being a heterocyclic or aromatic ring. The D-phenylglycine derivatives of both 7-aminocephalosporanic acid (cephaloglycin¹) and 7-aminodesacetoxycephalosporanic acid (cephalexin²) responded well (1, 2). These compounds (0.5–1.0 mg./ml. in water) reacted with acetone and sodium hydroxide at 100° to

form characteristic red chromophores. Ampicillin³ responded under the same conditions, but the sensitivity was not as great. Ampicillin must be present at approximately 50 times the concentration of cephalexin to give the same response in the test. Cephalexin and cephaloglycin (desacetyl cephaloglycin present as a degradation product) may be detected in urine at the concentration specified.

EXPERIMENTAL

Reagents—The following were used: acetone, reagent grade; and sodium hydroxide solution, 13.0% w/v.

Recommended Procedure—Transfer 2.0 ml. of aqueous sample (0.5–1.0 mg./ml.) to a test tube. Add 0.5 ml. of sodium hydroxide solution and 0.3 ml. of acetone. Mix and cover tube with a marble. Place in a boiling water bath for 3 min. The formation of a red color indicates the presence of a cephalosporin derivative having the following intact side chain in the 7-position: $\text{RCH}(\text{NH}_2)\text{CO}-$, R being a heterocyclic or aromatic ring. Determine the absorbance of the solution at 520 nm. after standing 3 min.

The sensitivity of this procedure was increased considerably (0.1–0.2 mg./ml.) by initially predegrading the sample under controlled conditions. Buffering the sample solution at pH 7 and allowing it to stand at 70° for 3 hr. were the conditions chosen for predegradation. The extent of color formation was found to be greater

¹ Cephaloglycin is the generic name for 7-(D- α -aminophenylacetamido)cephalosporanic acid.

² Cephalexin is the generic name for 7-(D- α -aminophenylacetamido)-desacetoxycephalosporanic acid.

³ Ampicillin is the generic name for 6-(D- α -aminophenylacetamido)-penicillanic acid.